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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,029	12/16/2005	Sally-Anne Stephenson	2381.0010000/MAC	9023

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,029	STEPHENSON, SALLY-ANNE	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *22-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending.

Applicant's election with traverse of Group I in the reply filed on November 20, 2007 is acknowledged. The traversal is on the ground(s) that searching all the groups would not be an undue burden. This is not found persuasive because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02). Upon review and reconsideration, Group II, claims 15-21 are rejoined with Group I, claims 1-14. Claims 22-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 1-21 are under prosecution.

Mark, priorty date matters when you have to decide 102b or 102a or in very rare cases, a breakthrough technology before or after their priority date, which becomes critical to evaluate the claimed invention for enablement. If there is no art rejection, do not make fuss about this. The battle between you and the attorney can go on forever for no good reaon.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method for inhibiting the proliferation of a cancer cell, inducing the death of a cancer cell and treating or preventing cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4. The claims read on a method of preventing or treating cancer in a subject.

The specification discloses that EphB4 expression was upregulated on colon and breast cancer cells. (Example 1) The specification also discloses that polyclonal antibodies to EphB4 induced cell death in breast and colon cancer cell lines. (Example 3). The specification further discloses that cell death by the polyclonal antibodies is inhibited by specific EphB4peptides. (Fig 14). The specification does not disclose any in vivo studies on the treatment of cancer with antibodies to EphB4.

Noren et al (Cancer Res, 2007, 67:3994-3997) disclose that the Eph receptors are present on most tissues. (page 3994, 1st column). Upregulated expression of EphB4 has been reported in types of cancer (page 3994, 1st column). Noren et al also states that the role of EphB4 in cancer is unknown and

that more research is needed to resolve the many confusing and controversial issues. (page 3997, 2nd column).

The claims of the instant application are not enabled because the teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for on a method of preventing or treating cancer in a subject. In particular, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para.

In addition, the treatment of disease with antibodies in vivo is generally unpredictable. White et al (Annu Rev Med 52:125-145, 2001) discloses that despite monoclonal antibody testing since the mid-1900's only in the past three years have some monoclonal antibodies provided sufficient efficacy as therapeutic agents (see Abstract). According to White et al, "The use of monoclonal antibodies for the treatment of carcinoma and hematologic malignancies is an evolving field". (see Conclusion). White et al discloses that numerous obstacles must be overcome for successful immunotherapy. These include choice of target antigen, immunogenicity of the antibodies, length of half-life and ability to recruit effector functions and antibody manufacturing.

Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity.

Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art and the specification recognize that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed antibody or variations of the antibody claimed could be effectively used for the treatment of any cancer. Although the tumor which was used to stimulate production of the claimed antibody clearly expresses the antigen, it is clear as set forth above, that it cannot be predicted, even when antigen is expressed that the claimed antibody would be effective for treating any cancer.

Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed antibodies would be effective for treatment in a subject based only on the ability of polyclonal antibodies to induce cell death in vitro.

Because of the known unpredictability of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the claimed antibody could function as claimed, that is could be used to treat cancer in a subject.

In addition, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined

and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells; A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

With regards to the prevention of cancer in a mammal comprising administering an antibody, the specification does not disclose sufficient guidance or objective evidence that such antibodies would predictably prevent the formation of cancer cells in a mammal. The prevention of cancer, let alone the prevention of cancer with an antibody, is highly unpredictable. The majority of studies suggest that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in *advance* of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. Further, such studies require the appropriate experimental models for analyzing chemo- or immunoprevention. For example, Granziero *et al.* (Eur. J. Immunol. 1999, 29:1127-1138) teach that many models are not suitable for testing immunotherapeutic approaches intended to cure cancer. They suggest that the optimal model (prostate cancer, in their case) would have spontaneous tumor development in its natural location (1st column, page 1128) wherein disease progression would closely resemble the progression of the particular type of cancer. Hence, depending on the type of model employed one could establish a reasonable link between antecedent drug and subsequent knowledge of the prevention of the disease. Further, reasonable guidance with respect to correlating agents that prevent cancer may depend upon quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. For example, Byers, T. (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventitive trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably

suggests that the claimed method would predictably prevent the formation of tumors in a mammal. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

It is apparent from the art that the treatment of cancer is unpredictable. As recently as 2007, Noren stated that it is unknown if EphB4 therapeutic will be effective in the treatment of cancer. (page 3007, 2nd column). All of this underscores the criticality of providing workable examples. However, there are no *in vivo* working examples for the treatment of cancer comprising administering an antibody to EphB4. The specification provides insufficient guidance with regard to these issues and provides no *in vivo* working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

Claims 5, 6, 7, 12, 13,14, 19, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5, 6, 7, 12, 13,14, 19, 20 and 21 are drawn to a genus of EphB4 peptides having a sequence having at least 85% identical to residues selected from the group consisting of residues 200 to 400 of EphB4 (SEQ ID NO: 1), residues 201 to 245 of EphB4 (SEQ ID NO: 1), residues 220 to 244 of EphB4 (SEQ ID NO: 1) and residues 220 to 230 of EphB4 (SEQ ID NO: 1), at least 90% identical to residues selected from the group consisting of residues 200 to 400 of EphB4 (SEQ ID NO: 1), residues 201 to 245 of EphB4 (SEQ ID NO: 1), residues

220 to 244 of EphB4 (SEQ ID NO: 1) and residues 220 to 230 of EphB4 (SEQ ID NO: 1), or peptides which have a substitution of amino acid Asp (D) to Asn (N) at residue 226 of EphB4. The specification discloses only one purified EphB4 protein with a sequence of SEQ ID NO:1..

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

The Federal Circuit has recently clarified that a molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of the genus of EphB4 peptides, per Lilly by structurally describing a representative number of EphB4 peptides that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of EphB4 peptides in a manner that satisfies either the Lilly or Enzo standards. There are insufficient structural features common to all members of the genus of polypeptide antagonists. The genus of genus of EphB4 peptides encompasses any number of peptides which may vary from SEQ ID NO:1 by up to 85%. This encompasses a multitude of EphB4 peptides, only one of which is identified in the instant specification. One species of EphB4 peptides, does not sufficiently describe the genus of EphB4 peptides and does not meet the standard set forth in Lilly.

The instant specification may also provide an adequate written description of the genus of polypeptide antagonists if the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The specification discloses only one protein species, SEQ ID NO:1. Thus, the specification does not describe sufficient structural characteristics that correlate with the ability of the genus of EphB4 peptides to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Thus, the specification does not provide an adequate written description of the genus of EphB4 peptides of claims 5, 6, 7, 12, 13,14, 19, 20 and 21 that is required to practice the claimed invention. Applicants have not described the genus of EphB4 peptides encompassed by claims 5, 6, 7, 12, 13,14, 19, 20 and 21 sufficiently to show they had possession of the claimed genus of EphB4 peptides .

Summary

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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